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Histological Scoring for Small Lung Adenocarcinomas 2 cm or Less in Diameter

A Reliable Prognostic Indicator

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Objective: Lung adenocarcinomas 2 cm or less in diameter were studied to develop histologic criteria predicting the outcome.

Materials and Methods: We reviewed 510 consecutive lung adenocarcinomas 2 cm or less in diameter and assessed three histologic parameters to implement a histologic scoring system: lymphovascular invasion, maximum diameter of the nonbronchioloalveolar carcinoma (BAC) component, and percentage of the solid, cribriform, and/or papillary component in the entire tumor volume (%solid/cribriform/papillary). One point was given to each of lymphovascular invasion-positive, non-BAC >10 mm and %solid/cribriform/papillary ≧30%, and by the sum of these points, a score of 0 to 3 was assigned for each tumor. We also evaluated minimally invasive adenocarcinomas comprising non-BAC ≦5 mm, Sakurai grades 1 and 2.

Results: Five-year disease-free survival rates of 287 patients with a histologic score of 0, 69 with a score of 1, 64 with a score of 2, and 90 with a score of 3 were 98.9%, 92.4%, 78.4%, and 54.0%, respectively. The 510 tumors included 129 noninvasive and 127 minimally invasive adenocarcinomas. None of these tumors recurred. In remaining 254 patients with overtly invasive adenocarcinomas, 5-year disease-free survival rates in 51 with a histologic score of 0, 49 with a score of 1, 64 with a score of 2, and 90 with a score of 3 were 95.9%, 89.2%, 79.4%, and 54.2%, respectively.

Conclusion: The histologic scoring system comprising lymphovascular invasion-positive, non-BAC >10 mm and %solid/cribriform/papillary ≧30% is able to predict the outcome of lung adenocarcinomas 2 cm or less in diameter not only in all cases but also in overtly invasive adenocarcinomas. Minimally invasive adenocarcinomas did not recur in this large series.

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Adenocarcinoma is the most frequent histologic type of lung cancer.[1] Because small peripheral adenocarcinomas are frequently encountered in Japan, the validity of limited surgery (segmentectomy or partial lung resection) for such tumors has recently been proposed. To qualify the need for limited surgery, it is mandatory to identify accurately low- and high-risk group of patients with small adenocarcinomas.

A number of histologic prognostic factors for small (≦3 or ≦2 cm) adenocarcinomas have been reported. Tumor, node, metastasis stage[2] is the most important prognostic factor,[3] even for small adenocarcinomas. Motoi et al.,[4] using predominant subtypes modified from the 2004 World Health Organization (WHO) classification,[5] recently reported that predominantly solid adenocarcinoma had a poor prognosis. It has also been reported that a predominantly papillary pattern or a certain amount of micropapillary pattern predicts poor outcome.[6,7]

In our institution, Shimosato et al.[8] reported scar grade in 1980, and Maeshima et al.[9] modified the scar grade in 2002. Kurokawa et al.[10] proposed "early" adenocarcinoma with no vascular invasion, low mitotic index, and lower scar grade (grade 1 or 2). Noguchi et al.[11] reported a 100% 5-year survival rate for patients with bronchioloalveolar carcinoma (BAC) and BAC with collapse, and a poor prognosis for pure solid, acinar (cribriform), and papillary adenocarcinoma. Yokose et al.[12] examined adenocarcinomas 3 cm or less in diameter and proposed an unfavorable subgroup showing vascular invasion or a papillary growth component exceeding 25%.

Previously proposed features of minimally invasive adenocarcinoma have included collapse and/or scar ≦5 mm,[13] invasion ≦5 mm,[14] and Sakurai grades 1 and 2.[15] Sakurai et al.[15] assessed adenocarcinomas 2 cm or less in diameter and demonstrated 100% 5-year disease-free survival rate in patients whose tumors showed stromal invasion in the area of bronchioloalveolar growth (grade 1) or stromal invasion localized at the periphery of a fibrotic focus (grade 2). Grade 1 tumors resemble BAC, and grade 2 tumors resemble BAC with collapse.

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In this study, we tried to clarify histologic risk factors of small lung adenocarcinomas by using a combination of three factors, which potentially helps define a subgroup benefiting best from the limited surgery: lymphovascular invasion, maximum diameter of the non-BAC component, and percentage of the solid, cribriform and/or papillary component in the entire tumor volume (%solid/cribriform/papillary). Moreover, we performed an additional examination for minimally invasive adenocarcinomas comprising a non-BAC component 5 mm or less in diameter (non-BAC ≦5 mm), Sakurai grades 1 and 2. The goal of this study was to stratify small lung adenocarcinomas 2 cm or less in diameter to predict outcome by using this histologic scoring system and clarify the criteria for minimally invasive and noninvasive adenocarcinomas.

PATIENTS AND METHODS

Patients

The study subjects were 510 consecutive adenocarcinomas of the lung 20 mm or less in diameter, surgically resected at the National Cancer Center Hospital, Japan, between 1997 and 2003. Clinical information was extracted from the medical records. Patients with synchronous multiple lung cancers were excluded. Four hundred one patients underwent lobectomy or more with complete lymph node dissection, 24 segmentectomy with lymph node sampling, and 85 segmentectomy or partial lung resection without lymph node dissection. Limited surgery was performed if tumors showed pure ground glass opacity by computed tomography or if patients had some clinical risks. All resected materials were pathologically proved to be free of tumor cells at the surgical margins. Tumor, node, metastasis stages were determined according to the Union Internationale Contre le Cancer (International Union Against Cancer) staging system,[2] except in patients without lymph node dissection. None of the patients received adjuvant treatment.

Pathologic Review

The materials were fixed in 10% formalin overnight. Tumors 20 mm or less (range: 5–20 mm) in diameter were cut at 5 mm intervals, which meant that one to four slides were prepared form each tumor according to size; i.e., one slide was made from a tumor 5 mm in diameter, two slides from a tumor 10 mm in diameter, three slides from a tumor 15 mm in diameter, and four slides from a tumor 20 mm in diameter. All slides of each tumor were observed for judgment of BAC or invasive adenocarcinoma.

We evaluated the prognostic impact of several histologic parameters, including lymphovascular invasion, maximum diameter of the non-BAC component, and %solid/cribriform/papillary. Histologic parameters were assessed after representative hematoxylin and eosin (HE)- and elastica-stained tumor slides had been reviewed. Overt lymphatic permeation and/or vascular invasion was judged to be lymphovascular invasion-positive and negative or suspicious but not definite as lymphovascular invasion negative.

The maximum diameter of the non-BAC component was measured on HE slides, because the definition of "invasion" is challenging, in terms of judgments of alveolar floating or filling tumor cells and collapse and/or scar (collapse/scar). For example, some pathologists consider alveolar floating or filling tumor cells showing a solid/cribriform/papillary pattern to represent invasion, whereas others consider this to represent noninvasion. The judgment of collapse/scar versus invasion with an acinar pattern is also problematic. Therefore, we simply measured the area that was not BAC. We considered non-BAC to include the area containing frank invasion (papillary, acinar, or solid component with a desmoplastic reaction), collapse, scar without tumor cells, and alveolar floating/filling tumor cells with micropapillary, cribriform, or solid pattern.

Because adenocarcinoma with a predominantly solid, cribriform, papillary, or micropapillary component was reported to have a poor prognosis,[4,6,7,11] the total percentage of these components in the entire tumor volume (%solid/cribriform/papillary) was measured semiquantitatively. One point was assigned for tumors showing each of lymphovascular invasion-positive, non-BAC >10 mm, and %solid/cribriform/papillary ≧30%, to give a total of 0 to 3 points (Table 1). According to the histologic score given by the sum of the points, clinical outcomes were compared.

We also evaluated the prognosis of noninvasive adenocarcinoma comprising BAC and BAC with collapse and minimally invasive adenocarcioma comprising non-BAC ≦5 mm, Sakurai grades 1 and 2. Simultaneously, we evaluated the scar grade,[8] the Noguchi classification,[11] and the 2004 WHO predominant subtype.[4]

Statistical Analysis

Five-year disease-free survival rates were calculated by the Kaplan-Meier method. Differences in survival curves were compared using the log-rank test. Multivariate analysis was performed using Cox proportional hazards analysis. Differences were considered significant at $p < 0.05$.

RESULTS

Patient Characteristics

The patients' clinicopathological features are summarized in Table 2. Outcome was better in patients who underwent limited surgery than in those who underwent lobectomy or more ($p = 0.0360$), perhaps due to the fact that many of the tumors showing predominantly ground glass opacity by com-

TABLE 1. Histological Scoring System for Small Lung Adenocarcinoma

A. Lymphovascular invasion	Positive	+1 point
	Negative	0 point
B. Non-BAC size	>10 mm	+1 point
	≦10 mm	0 point
C. %solid/cribriform/papillary	≧30%	+1 point
	<30%	0 point
A + B + C		0–3 points

BAC, bronchioloalveolar carcinoma; %solid/cribriform/papillary, percentage of solid, cribriform, and/or papillary component in the entire tumor volume.

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TABLE 2. Patient Characteristics

Parameter	No. of Patients (%)	5-yr Disease-Free Survival (%)	*P*
Total	510	87.6	
Gender			
Male	230 (45)	86.2	NS
Female	280 (55)	88.9	
Age (yr, median)			
23–89 (62)			
Operation			
Lobectomy or more	401 (79)	85.4	0.0361
Segmentectomy	25 (5)	95.8	
Partial lung resection	84 (16)	96.2	
Pathological stage[a]			
I	352 (83)	93.7	<0.0001
II–IV	70 (17)	46.9	
Tumor size			
5 to ≦10 mm	99 (19)	96.7	0.0040
10 to ≦15 mm	187 (37)	88.3	
15 to ≦20 mm	224 (44)	83.2	
Lymph node metastasis[a]			
Negative	356 (84)	92.6	<0.0001
Positive	66 (16)	49.2	
Lymphovascular invasion			
Negative	361 (71)	97.9	<0.0001
Positive	149 (29)	62.6	
Scar grade			
1	75 (15)	100	
2	139 (27)	99.3	<0.0001
3	285 (56)	79.5	
4	11 (2)	67.5	
Noguchi classification			
Types A–B	129 (25)	100	
Type C	323 (63)	85.8	<0.0001
Type D	34 (7)	78.4	
Type E	10 (2)	58.3	
Type F	14 (3)	61.2	
WHO predominant subtype			
BAC	353 (69)	95.4	<0.0001
Acinar	22 (4)	68.3	
Papillary	58 (12)	69.0	
Solid	77 (15)	70.8	

[a] Among 422 patients treated by lymph node dissection.
WHO, World Health Organization; NS, not significant.

puted tomography were treated by limited surgery. All the patients who underwent lobectomy or more (401 patients) and those who underwent segmentectomy with lymph node sampling (21 patients) were evaluable for pathologic stage: 347 tumors were p-stage IA, five were IB, 26 were IIA, five were IIB, 26 were IIIA, 11 were IIIB, and two were IV. Five-year disease-free survival rate for 510 patients was 87.6%. Tumors recurred in 66 patients. The sites of initial recurrence were the lung in 20 patients, hilar, mediastinal, or cervical lymph nodes in 17, bone in 18, pleura in 11, brain in 12, liver in two, adrenal gland in two, and spleen in one. Because the tumors in this study ranged from 5 to 20 mm in diameter, we compared patient survivals among three tumor size groups: tumors 5 to ≦10 mm in diameter (99 cases), tumors 10 to ≦15 mm in diameter (187 cases), and tumors 15 to ≦20 mm in diameter (224 cases), and the 5-year disease-free survival rates for these groups were 96.7%, 88.3%, and 83.2%, respectively. The survival rates for patients with tumors 5 to ≦10 mm in diameter and those with 15 to ≦20 mm in diameter differed significantly.

Histologic Examinations

The correlation of histologic parameters and clinical outcome of all 510 patients are summarized in Tables 3 and 4. Five-year disease-free survival rate was 97.9% in the 361 patients who were lymphovascular invasion-negative and 62.6% in the 149 patients who were lymphovascular invasion-positive. Patients with lymphovascular invasion positivity had a significantly worse outcome than those with negativity ($p < 0.0001$). Non-BAC size was 0 mm in 61 patients, 0 to ≦5 mm in 122, 5 to ≦10 mm in 180, and >10 mm in 147, the respective 5-year disease-free survival rate being 100%, 100%, 91.0%, and 67.7%. Among 122 tumors with a non-BAC component of 0 to ≦5 mm, 42 were BAC with collapse and 80 were invasive adenocarcinomas; none of these tumors recurred. Five-year disease-free survival rate in patients with non-BAC >10 mm had a significantly worse outcome than those with non-BAC 5 to ≦10 mm ($p < 0.0001$).

%Solid/cribriform/papillary was <30% in 339 patients and ≧30% in 171, with 5-year disease-free survival rate of 96.9% and 68.9%, respectively, the latter being significantly worse than the former ($p < 0.0001$). Five-year disease-free survival rate was examined in relation to %solid/cribriform/papillary using a cut-off value of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90%, and the 30% cut off was found to have the highest statistical significance (data not shown).

Five-year disease-free survival rate was 98.9% in 287 patients with a histologic score of 0, 92.4% in 69 patients

TABLE 3. Correlation of Histological Parameters and Score with Clinical Outcome in All 510 Patients with Small Lung Adenocarcinoma

Parameters	Subgroups	No. of Patients (%)	5-yr Disease-Free Survival (%)	*P*
Total		510	87.6	
Lymphovascular invasion	Negative	361 (71)	97.9	<0.0001
	Positive	149 (29)	62.6	
Non-BAC size (mm)	0	61 (12)	100	
	0 to ≦5	122 (24)	100	
	5 to ≦10	180 (35)	91.0	<0.0001
	>10	147 (29)	67.7	
%solid/cribriform/papillary	<30	339 (66)	96.9	<0.0001
	≧30	171 (34)	68.9	
Histological score	0	287 (56)	98.9	
	1	69 (13)	92.4	<0.0001
	2	64 (13)	78.4	
	3	90 (18)	54.0	

BAC, bronchioloalveolar carcinoma; %solid/cribriform/papillary, percentage of solid, cribriform, and/or papillary component in the entire tumor volume.

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TABLE 4. Survival of Patients with BAC, Minimally Invasive, and Overtly Invasive Adenocarcinoma

Invasiveness	No. of Patients (%)	5-yr Disease-Free Survival (%)	P
Total	510	87.6	
Noninvasive adenocarcinoma	129 (25)	100	
BAC	61 (12)		
BAC with collapse	68 (13)		
Minimally invasive adenocarcinoma[a]	127 (25)	100	
Non-BAC ≦5 mm	80 (16)		
Sakurai grade 1	10 (2)		
Sakurai grade 2	80 (16)		
Overtly invasive adenocarcinoma	254 (50)	75.7	
Histological score 0	51 (10)	95.9	
Histological score 1	49 (10)	89.2	<0.0001
Histological score 2	64 (12)	79.4	
Histological score 3	90 (18)	54.2	

[a] Minimally invasive categories were not mutually exclusive but rather different ways of stratification. All the Sakurai grade 1 tumors and 41% (33/80) of the Sakurai grade 2 tumors simultaneously fulfilled the criteria of non-BAC ≦5 mm.

BAC, bronchioloalveolar carcinoma.

with a score of 1, 78.4% in 64 patients with a score of 2, and 54.0% in 90 patients with a score of 3. Five-year disease-free survival rate in patients with histologic scores of 2 and 3 was worse than that of patients with scores of 0 and 1 ($p < 0.0001$) (Figures 1 and 2).

Among the 510 tumors, 61 were classified as BAC, 68 as BAC with collapse, 80 as invasive adenocarcinoma with non-BAC ≦5 mm, 10 as Sakurai grade 1, and 80 as Sakurai grade 2 (Table 4). Among 80 invasive adenocarcinomas with non-BAC ≦5 mm, two showed lymphovascular invasion-positive and three had %solid/cribriform/papillary ≧30%. Minimally invasive categories were not mutually exclusive. All 10 Sakurai grade 1 tumors showed non-BAC ≦5 mm and were able to be included in the category of non-BAC ≦5 mm. Among 80 Sakurai grade 2 tumors, 33 showed non-BAC ≦5 mm, 38 showed non-BAC 5 to ≦10 mm, and nine showed non-BAC >10 mm. None of Sakurai grade 1 or 2 tumors showed lymphovascular invasion-positive or %solid/cribriform/papillary ≧30%.

Among 254 overtly invasive adenocarcinomas after excluding the above-mentioned noninvasive and minimally invasive adenocarcinomas, 5-year disease-free survival rate was 96% in 51 patients with a tumor score of 0, 89% in 49 patients with a tumor score of 1, 78% in 64 patients with a tumor score of 2, and 54% in 90 patients with a tumor score of 3. (Figure 3) Because 5-year disease-free survival rates differed significantly between tumors with histologic scores of 0 and 1, and those of 2 and 3 ($p < 0.0001$), the present histologic scoring system seems to be useful for risk evaluation of overtly invasive adenocarcinomas.

Simultaneously, the scar grade,[8] the Noguchi classification,[11] and the WHO predominant subtype[4] were examined by univariate analysis (Table 2). Scar grade was able to predict the outcome of patients with adenocarcinomas 2 cm or less in diameter. Use of the Noguchi classification revealed that patients with types D, E, and F tumors had a worse prognosis than those with type C tumors ($p < 0.0001$). However, the numbers of type D, E, and F tumors were relatively small, and the majority were classified as type C. Among the total of 58 types D, E, and F tumors, four scored 1, 15 scored 2, and 39 scored 3, and thus, the majority were classified a score of 2 or 3. Use of the WHO predominant subtype revealed that patients with BAC-predominant tumors had a better outcome than the others ($p < 0.0001$). Multivariate analysis showed that histologic score, pathologic stage, lymph node metastasis, and WHO predominant subtype were statistically significant (Table 5).

DISCUSSION

Recently, adenocarcinoma has become the most frequent histologic type of lung cancer.[1] Because small adenocarcinomas are frequently encountered in Japan, the validity of limited surgery has recently been proposed. Risk assessment of detailed histologic examination of small adenocarcinomas is needed to qualify the adequacy of limited surgery.

It has been reported that approximately 20% of adenocarcinomas 20 mm or less in diameter had lymph node metastasis.[16] In this study, 16% of a total of 510 adenocarcinomas 20 mm or less in diameter has lymph node metastasis, which was slightly lower than in the previous reports. Although the 5-year disease-free survival of patients with adenocarcinomas 20 mm or less in diameter has not been sufficiently assessed, Sakurai et al.[15] reported a figure of 76.4% on the bases of 380 cases. The patients in this study had a 5-year disease-free survival of 87.6%, which was a higher rate than that reported by Sakurai et al.

A number of reports have addressed the outcome of BAC. For resected localized BAC, the 5-year disease-free survival rate was reported to be 73% by Volpino et al.[17] in 2001, 74% by Breathnach et al.[18] in 2001, and 81% by Rena et al.[19] in 2003. At our institution, the survival of patients with localized BAC was reported to be 100% by Sakurai et al.[15] in 2004 and Maeshima et al.[9] in 2003. A data have indicated that the survival of patients with BAC improved after revision of the BAC criteria in the 1999 WHO classification, which defined BAC only as pure BAC, not including mixed adenocarcinoma with a BAC component.[20]

We were able to verify several prior reports. As shown in Table 2, scar grade proposed by Shimosato et al.[8] was able to predict the outcome of patients with adenocarcinomas 2 cm or less in diameter. However, there were some problems in that, a proportion of papillary adenocarcinomas, a high-risk subgroup, were included as scar grade 1 tumors. Therefore, a small number of grade 1 tumors recurred. In addition, distinction between grades 2 and 3 was not clear.

The Noguchi classification[11] was also able to predict the outcome of patients with small adenocarcinomas, because types D, E, and F tumors showed a worse outcome than the others. However, the majority of small adenocarcinomas were classified as type C, and thus subclassification of type C tumors does seem necessary. Although original article by Noguchi et al. included invasive adenocarcinomas with lym-

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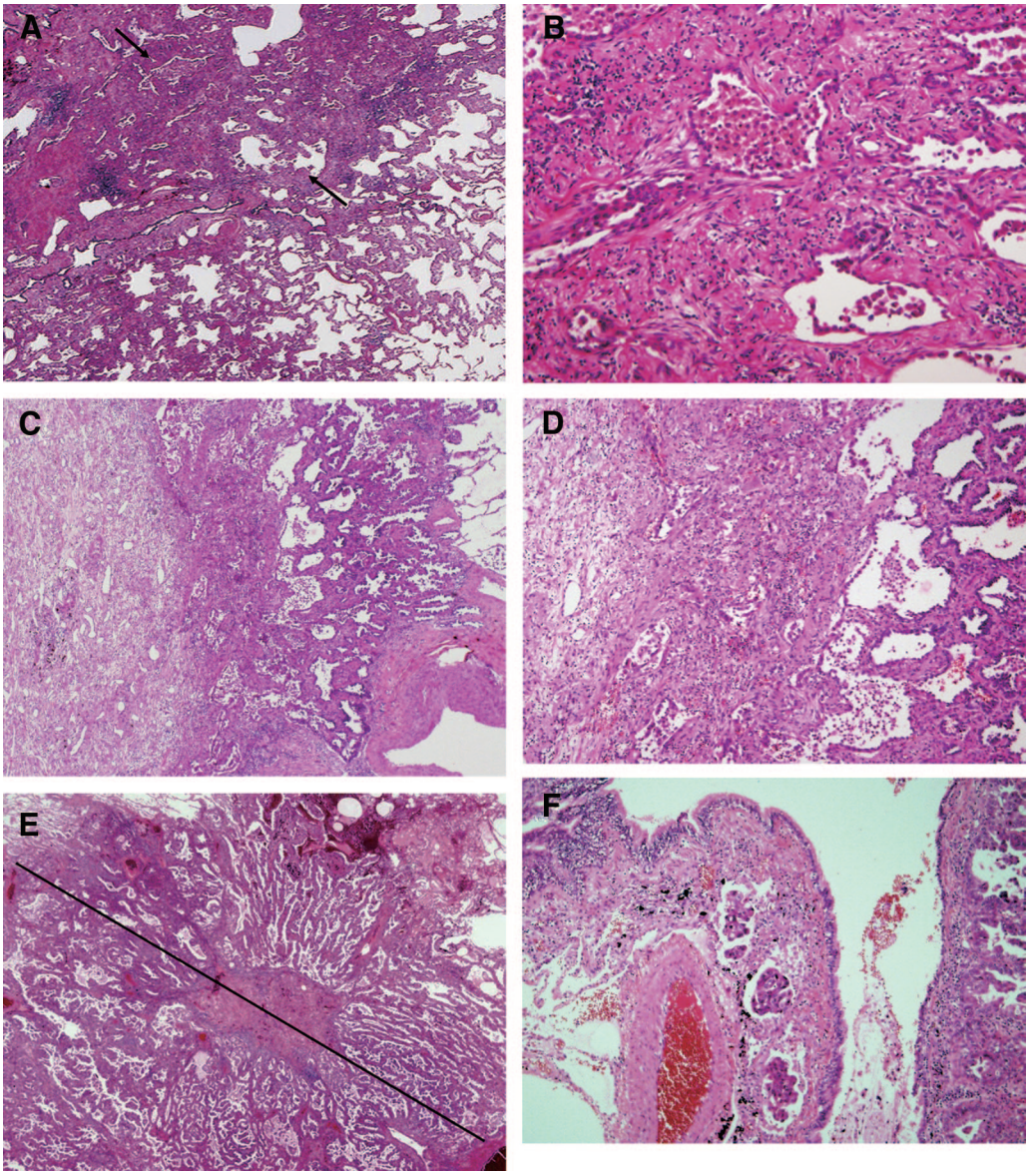

FIGURE 1. Histology of Sakurai grades 1 and 2 and a histologic score 3 tumor. *A*, Sakurai grade 1 resembles bronchioloalveolar carcinoma (BAC) in low-power view (hematoxylin and eosin [HE], ×40). *B*, Sakurai grade 1 has a small invasive focus in the alveolar area (HE, ×400). *C*, Sakurai grade 2 resembles BAC with collapse in low-power view (HE, ×40). *D*, Sakurai grade 2 shows a fibroblastic reaction only at the interface between BAC and collapse (HE, ×200). *E*, *F*, An example of a score 3 tumor. The tumor shows non-BAC >10 mm, %solid/cribriform/papillary ≧30% (*E*, HE, ×12.5), and lymphovascular invasion positivity (*F*, HE, ×100). Both scar and a papillary component were counted as non-BAC.

phovascular or pleural invasion in almost 10% of types A and B tumors, in this study, BAC and BAC with collapse included only noninvasive adenocarcinomas. We also assessed the WHO predominant subtype.[4] The BAC-predominant subtype was the largest subtype and showed a better prognosis than the others. Because most tumors have been classified as the BAC-predominant subtype in Japanese series, subclassification of this subtype is needed.

In this study, we performed histologic prognostic subclassification of small adenocarcinomas using three indicators. Simultaneously, we performed an additional examination for prognostic implication of minimally invasive adenocarcinoma proposed by our institution previously. Non-BAC ≦5 mm, which is a modification of ≦5 mm collapse/scar[13] and ≦5 mm invasion,[14] Sakurai grades 1 and 2,[15] was assessed using a larger series.

Kurokawa et al.[10] and Yokose et al.[12] reported that vascular invasion was a poor prognostic indicator in small adenocarcinomas. Because we considered that lymphovascular invasion was one of the results of invasion and reflected metastatic potential, we assumed that it must be the most important prognostic indicator.

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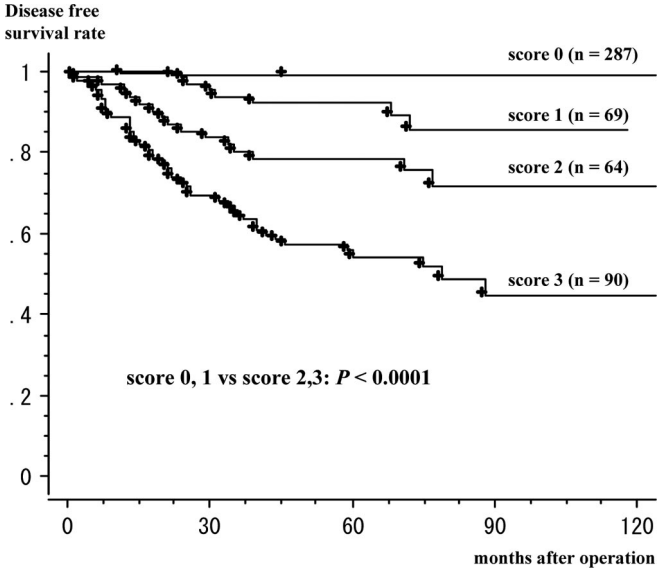

FIGURE 2. Survival curves for all 510 patients stratified by histologic score.

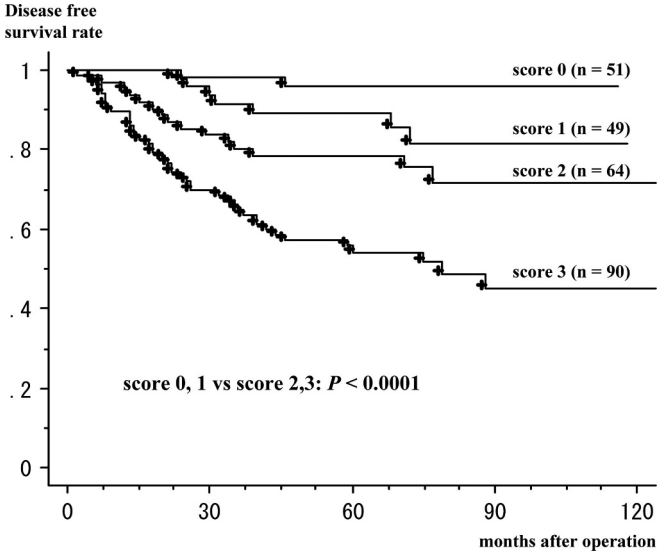

FIGURE 3. Survival curves for 242 patients with overtly invasive adenocarcinomas stratified by histologic score.

Noguchi et al.[11] reported that pure solid, acinar (cribriform), or papillary adenocarcinoma had poor prognosis. Motoi et al.[4] reported that the solid-predominant subtype had a poor prognosis on the basis of the 2004 WHO predominant subtype classification. Moreover, predominantly, papillary adenocarcinoma[7] and adenocarcinoma with a certain amount of micropapillary pattern[6] have been reported to have a poor prognosis. Therefore, we considered all the papillary (including micropapillary) cribriform, and solid components to be poor prognostic factors possibly indicative of invasive quality and assessed %solid/cribriform/papillary.

The size of invasion is also a prognostic indicator, as shown in reports of modified scar grade,[9] ≦5 mm invasion,[14] <6 mm invasion,[21] and ≦5 mm collapse/scar[13] and may reflect invasive quantity. However, because definition of invasion and collapse/scar is somewhat obscure, we examined non-BAC size, which includes frank invasion, scar/collapse, and alveolar floating/filling tumor cells. We considered that assessment of these three indicators in combination—lymphovascular invasion, non-BAC size, and %solid/cribriform/papillary—could predict outcome in detail and examined them by using a large series.

TABLE 5. Results of Multivariate Analysis Using the Cox Proportional Hazards Model

Variables	*P*	HR	95% CI
Histological score	<0.0001	3.175	2.093–4.816
Pathological stage	<0.0001	4.005	2.455–6.534
Lymph node metastasis	0.0210	1.341	1.137–1.850
WHO predominant classification	0.0232	1.743	1.575–1.960

Gender, age, operation method, tumor size, scar grade, and Noguchi classification were also examined, but these variables were not selected.
HR, hazard ratio; CI, confidence interval.

Three indicators of poor prognosis, lymphovascular invasion-positive, non-BAC >10 mm, and %solid/cribriform/papillary ≧ 30%, were used to assign a score that would subclassify and predict outcome in patients with small adenocarcinomas. The scoring system was also applied to 254 overtly invasive adenocarcinomas after excluding BAC, BAC with collapse, and minimally invasive adenocarcinoma. Because the patient group with a histologic score of 0 had 95.9% 5-year disease-free survival rate, the validity of limited surgery for that group may be qualified. Patients with a histologic score of 1 might also be candidates for limited surgery, whereas patients with scores of 2 and 3 should not undergo limited surgery from the viewpoint of high recurrence risk.

We reevaluated minimally invasive adenocarcinomas reported from our institution using a larger series. None of 80 patients with invasive adenocarcinomas with non-BAC ≦5 mm suffered recurrence. However, as two cases with non-BAC ≦5 mm were lymphovascular invasion positive, a small number of non-BAC ≦5 mm tumors might have metastatic potential, and therefore, careful follow-up will be needed in the future. Also, none of 10 patients with Sakurai grades 1 and 80 patients with Sakurai grade 2 suffered recurrence. From these results, as reported from our institution previously, we concluded that tumors with non-BAC ≦5 mm, Sakurai grade 1 or 2 can be considered minimally invasive adenocarcinomas. However, because all cases of Sakurai grade 1 simultaneously fulfilled the criteria of non-BAC ≦5 mm, only non-BAC ≦5 mm and Sakurai grade 2 should be retained as minimally invasive adenocarcinoma. Finally, in this study, we gained an impression that surgical specimens of noninvasive and minimally invasive adenocarcinoma had been increasing recently.

From our findings, we are able to derive two main conclusions. First, the outcome of patients with adenocarcinomas 2 cm or less in diameter is predictable by using the histologic scoring system comprising lymphovascular invasion-positive, non-BAC >10 mm and %solid/cribriform/papillary ≧30%. Second, it was reconfirmed that patients whose

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tumors had non-BAC ≦5 mm, Sakurai grades 1 and 2 showed 100% survival. Patients with noninvasive, minimally invasive, or histologic score 0 adenocarcinomas may be candidates for limited surgery, whereas it seems problematic to conduct limited surgery for histologic score 2 or 3 adenocarcinomas. The histologic scoring system and minimally invasive categories might be useful only for small adenocarcinomas.

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